

## REVIEW ARTICLE

# The 2022 symposium on dementia and brain aging in low- and middle-income countries: Highlights on research, diagnosis, care, and impact

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**Abstract**

Two of every three persons living with dementia reside in low- and middle-income countries (LMICs). The projected increase in global dementia rates is expected to affect LMICs disproportionately. However, the majority of global dementia care costs occur in high-income countries (HICs), with dementia research predominantly focusing on HICs. This imbalance necessitates LMIC-focused research to ensure that characterization of dementia accurately reflects the involvement and specificities of diverse populations. Development of effective preventive, diagnostic, and therapeutic approaches for dementia in LMICs requires targeted, personalized, and harmonized efforts. Our article represents timely discussions at the 2022 Symposium on Dementia and Brain Aging in LMICs that identified the foremost opportunities to advance dementia research, differential diagnosis, use of neuropsychometric tools, awareness, and treatment options. We highlight key topics discussed at the meeting and provide future recommendations to foster a more equitable landscape for dementia prevention, diagnosis, care, policy, and management in LMICs.

**KEYWORDS**

Alzheimer's disease, dementia, diversity, high-income countries, low- and middle-income countries, risk factors, vascular dementia

**Highlights**

- Two-thirds of persons with dementia live in LMICs, yet research and costs are skewed toward HICs.
- LMICs expect dementia prevalence to more than double, accompanied by socioeconomic disparities.
- The 2022 Symposium on Dementia in LMICs addressed advances in research, diagnosis, prevention, and policy.
- The Nairobi Declaration urges global action to enhance dementia outcomes in LMICs.

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## 1 | INTRODUCTION

Approximately 50 million people worldwide have dementia, an estimate projected to reach nearly 150 million by 2050.<sup>1</sup> Current prevalence estimates suggest two of every three people living with dementia (PLWD) reside in low- and middle-income countries (LMIC) (Figure 1). Of concern, the number of PLWD in LMICs is projected to more than double.<sup>1,2</sup> These increases can be largely attributed to population growth and the shift in population structure toward older adults. While population growth is projected to be imperative in sub-Saharan Africa (SSA), population aging per se is also an important contributory factor in East Asia.<sup>1</sup> Socioeconomic disparities underlying LMICs are a critical factor impacting the understanding of dementia in terms of risk factors and care of patients.<sup>3,4</sup>

In 2019, the worldwide cost of dementia was estimated at USD1.3 trillion, and this figure could reach more than USD2 trillion by 2030. However, these estimates are mostly driven by HICs.<sup>6</sup> In fact, predictive models show 74% of the estimated global dementia cost occurs in HICs, despite the fact that most PLWD reside in LMICs.<sup>7</sup> In LMICs, family care accounts for 65% of the dementia cost, while direct medical care and social care account for only 35%. In contrast, informal care accounts for 44% of dementia costs in HICs.<sup>7</sup> In regions such as Latin America, caregiver burden is among the largest in the world and more strongly affected by gender disparities.<sup>8</sup> These figures may reflect under- or misdiagnosis of dementia and poor availability and access to dementia care services in LMICs.<sup>9</sup>

Key common factors across LMICs that could contribute to the lived experience of dementia in these regions include low public awareness of dementia, high stigma and misconceptions, low literacy, insufficient dementia-related knowledge and training among professionals and caregivers, poor interprofessional cooperation, inappropriate predictive and analytical care models, and lack of equitable access to suitable services.<sup>10,11</sup> Recognizing the importance of such challenges, the World Health Organization (WHO) has developed the "Global Action Plan on the Public Health Response to Dementia 2017 – 2025," which aims to provide policymakers and dementia experts with a roadmap to address dementia globally and regionally.<sup>12</sup> However, the WHO's 2021 report showed that most LMICs do not currently have a national dementia plan, highlighting insufficient progress in addressing the global dementia action plan by 2050.<sup>7,13</sup>

An important challenge in addressing the impact of dementia in LMICs is the underrepresentation of ethnically and geographically diverse individuals in research studies. Dementia research is mostly conducted in HICs, where only 18% of the world's aging population resides.<sup>14</sup> Only a fraction of dementia clinical trials are conducted in LMICs, limiting the participation of populations from these countries<sup>15,16</sup> (Figure 2). Consequently, the results of trials conducted in HICs may not be directly applicable to LMICs, due to differences in disease profiles and severity, healthcare access, affordability, infrastructure, skills, and other resources. Determinants of healthy aging are highly heterogeneous according to regional diversity, calling for urgent tailored perspectives in global approaches.<sup>4</sup> Furthermore, biological

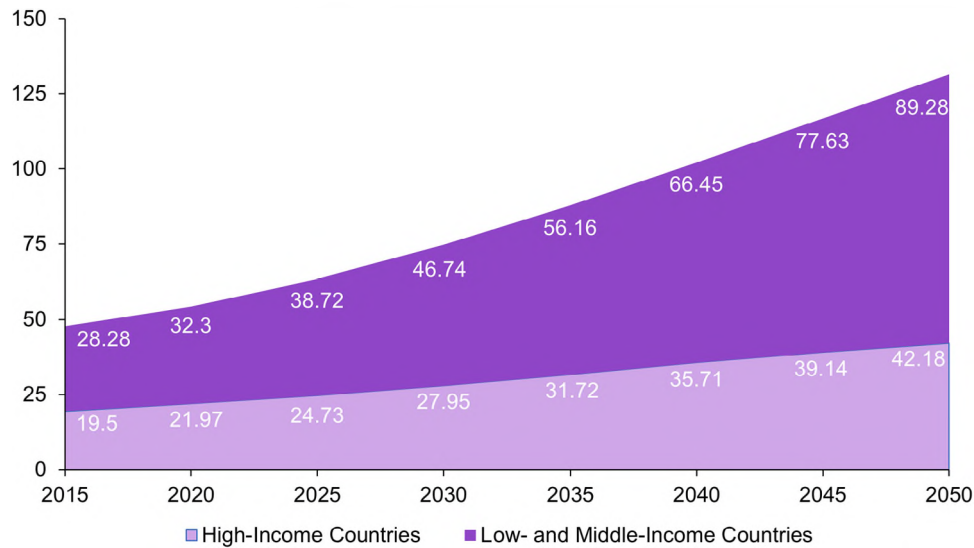
### RESEARCH IN CONTEXT

- 1. Systematic review:** Emerging findings suggest that the projected increase in global dementia rates is expected to affect low- and middle-income countries (LMICs) disproportionately, yet most resources are allocated to high-income countries (HICs). The authors of this article highlight advances in dementia research, issues in diagnosis, and care of dementia patients discussed at the 2022 Symposium on Dementia and Brain Aging in LMICs, held in December 2022 in Nairobi, Kenya.
- 2. Interpretation:** Research presented at the symposium highlighted the importance of LMIC-focused research to ensure that characterization of dementia accurately reflects the involvement and specificities of diverse populations.
- 3. Future directions:** A multifaceted approach is necessary to reduce the impact of dementia in LMICs that involves developing and promoting national dementia plans, robust policies, inclusive research, and building capacity. These and other recommendations were set forth by the Nairobi Declaration with the aim of improving dementia prevalence, outcomes, and personal and societal impacts in LMICs.

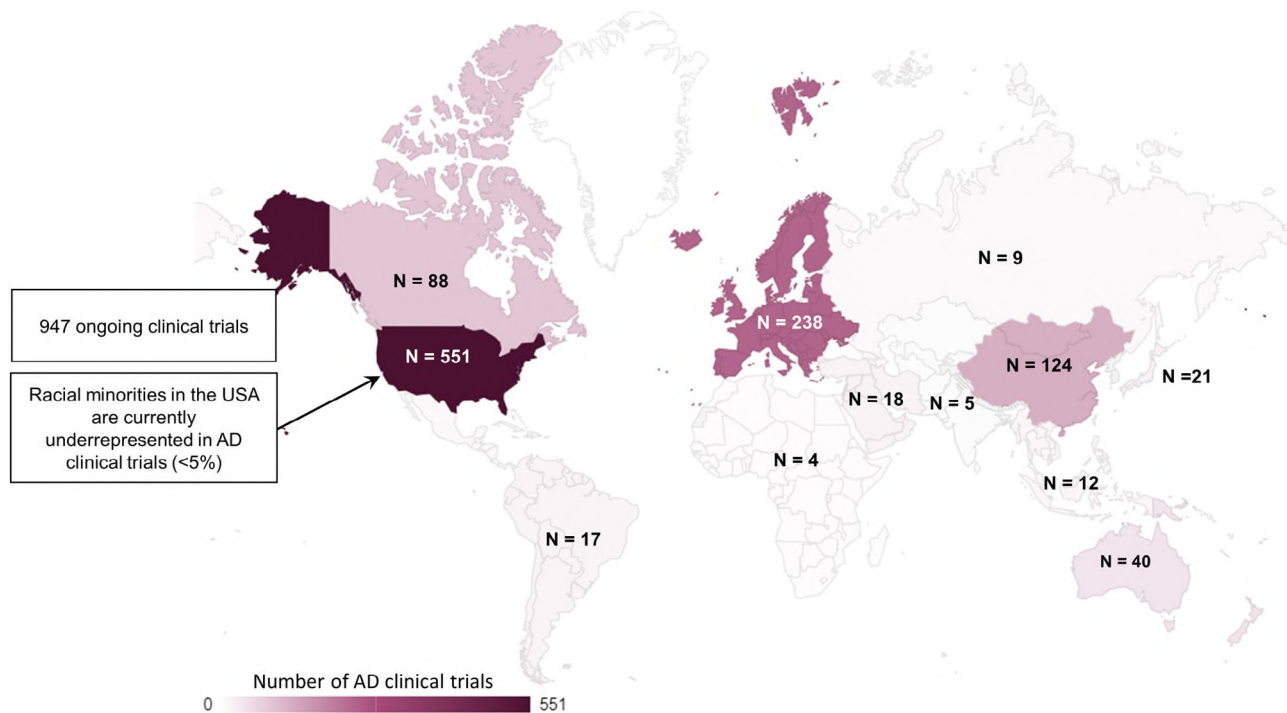
and genetic variations across populations may influence treatment responses and the frequency of adverse events to investigational products.<sup>17–19</sup>

Limited dementia research conducted in LMICs may also narrow the scope of studies away from questions particularly relevant to the LMICs. For example, Alzheimer's disease (AD) accounts for around 60% of all dementia in HICs, while vascular dementia (VaD) accounts for only 15%. However, in LMICs, VaD constitutes about 30% of dementia cases.<sup>20,21</sup> Furthermore, the apolipoprotein E (APOE) genotype may modify dementia risk differently based on ancestral backgrounds.<sup>22,23</sup> Thus, developing preventive and therapeutic strategies for dementia in LMICs requires consideration of the unique environmental factors and the genetic diversity in these regions. Aging populations in LMICs often differ markedly in culture, living environment, and resources, requiring not only rigorous but disparate approaches to research. It is also not unlikely that cycles of infectious diseases such as the COVID-19 pandemic will modify the overall burden of dementia, not only in LMICs but globally.<sup>24,25</sup>

In light of these and other challenges, the 2022 Symposium on Dementia and Brain Aging in LMICs, held in Nairobi, Kenya, focused on relevant advances in dementia research, diagnosis, prevention, policy, and care in LMICs. The aim was also to foster national and international collaboration in LMICs. The symposium was convened by the Alzheimer's Association (USA), Newcastle University (UK), and the University of Texas Rio Grande Valley (USA) and funded in part by the



**FIGURE 1** Projected prevalence of dementia cases in LMICs compared to HICs. Graph labels: x-axis shows year; y-axis represents numbers in millions. Data modified from Wimo et al. (2018).<sup>5</sup>



**FIGURE 2** Differential numbers of pharmacological clinical trials in AD between LMICs and HICs. Compiled by R Allegri, Argentina, 2022 using data from clinicaltrials.gov.

National Institute on Aging (NIA), USA. Several specific topics, such as cost of dementia and prevalence in LMICs, VaD, and stroke, movement disorders, language and aphasia, genetics, modifiable risk factors, human immunodeficiency virus, dementia care, and policy were discussed by invited experts. In this review, we provide a summary of the topics, highlighting the urgent need for targeted efforts to address the dementia burden in LMICs.

## 2 | MODIFIABLE RISK FACTORS FOR DEMENTIA

A growing number of studies indicate stable or declining incidence and prevalence of dementia in HICs over the last 25 years.<sup>26,27</sup> Decline in dementia rates has been attributed mainly to improved cardiovascular health due to lifestyle changes, improved social and welfare systems, prompt diagnosis and treatment of comorbidities, greater access to

medication, and increasing education levels. Such promising findings suggest that identifying and targeting modifiable risk factors may be effective strategies to reduce risk for dementia.<sup>27</sup> In contrast, current evidence suggests that dementia rates in low-resource settings, including in LMICs, are not declining but expected to even rise steadily, as indicated by the estimated projections up to 2050.<sup>27</sup> While up to 40% of dementia cases worldwide have been attributed to the 12 modifiable risk factors identified by the 2020 Lancet Commission,<sup>28</sup> the population attributable fraction (PAF) – the fraction that is theoretically prevented by eliminating risk factors – varies greatly between LMICs and HICs.<sup>29,30</sup>

Cross-sectional data from the 10/66 Dementia Research surveys have permitted the PAF for dementia associated with nine modifiable risk factors to be calculated in select LMICs, including China, India, and Latin American countries. The modifiable risk factors included lower early-life education, midlife hearing loss, hypertension, obesity, later-life smoking, depression, physical inactivity, social isolation, and diabetes. The results showed that the PAF for dementia was 39.5% in China, 41.2% in India, and 55.8% in Latin America. Furthermore, five risk factors were more prevalent in these LMICs than worldwide estimates, including less childhood education, smoking, hypertension, obesity, and diabetes.<sup>29</sup> Importantly, risk models from global settings may not simply be extrapolated to LMICs.<sup>31</sup> Within Latin America, researchers analyzing longitudinal data from the Brazilian Longitudinal Study of Aging (ELSI-Brazil) study observed varying PAF for different regions of Brazil.<sup>30</sup> The 12 modifiable risk factors for dementia accounted for 54% of the cases in poorer regions of Brazil versus 49% in wealthier regions, with less education, hypertension, and hearing loss being the most important risk factors.<sup>30</sup> New reports on risk factors in Latin America and Indonesia reveal a larger involvement of factors related to social and health disparities than factors such as age or gender.<sup>32,33</sup>

Together, these findings indicate that a higher percentage of dementia cases may be attributed to modifiable risk factors in LMICs than in HICs. Therefore, the potential for dementia prevention by addressing modifiable risk factors is particularly significant for LMICs. As many risk factors can cluster,<sup>34–37</sup> implementing effective policy interventions that enhance access to healthy foods, promote physical activity, and address social and economic disparities in LMICs is crucial. Furthermore, population-based strategies that utilize pragmatic, broadly applied, and low-cost interventions are needed. As an example, the Latin American Initiative for Lifestyle Intervention to Prevent Cognitive Decline (LatAm-FINGERS) trial is a randomized controlled trial for dementia prevention that simultaneously targets multiple modifiable risk factors.<sup>38</sup> Similarly, the ongoing World-Wide FINGERS in Africa (AFRICA-FINGERS) project aims to assess culturally informed multimodal intervention strategies for promoting brain health in indigenous African elders at risk of dementia and assess barriers to adherence and sustainability of the intervention via a precision-prevention framework. At the 2022 symposium, the role of several modifiable risk factors for dementia within LMICs was highlighted. In what follows, we provide a summary of some of these important results.

## 2.1 | Diet

Observational studies indicate that a healthy diet throughout life is essential for maintaining optimal brain health, particularly vascular brain health.<sup>39</sup> Individual dietary components such as fruits, vegetables, and fish have been linked with a lower risk of dementia and slower memory decline<sup>40</sup> and possibly decreased brain amyloid beta (A $\beta$ ) accumulation.<sup>41</sup> Dietary patterns such as the Mediterranean diet (MEDi diet) and Dietary Approaches to Stop Hypertension (DASH diet) have been associated with reduced risk of dementia and AD and lower rates of cognitive decline in some studies.<sup>42</sup> Such dietary patterns emphasize a high intake of plant-based foods and low saturated lipids and red meat consumption.<sup>40,43</sup> However, adherence to the MEDi and DASH Diet Intervention (MIND) may be influenced by individual income, evident in some countries like Brazil.<sup>44</sup> This implies the need for more affordable dietary interventions in LMICs.

While diets rich in whole grains, fruit, and legumes have been linked with dementia risk in some studies, the burden of non-communicable chronic disease due to low dietary fiber in SSA has increased substantially between 1990 and 2019.<sup>45</sup> A study in the Central African Republic showed that reduced consumption of oleaginous foods was associated with a 3.7- and 2.8-fold higher risk of mild cognitive impairment (MCI) and dementia, respectively.<sup>46</sup> The rising consumption of ultra-processed foods, which is associated with cognitive decline, is a concerning trend in LMICs.<sup>47</sup> Furthermore, while higher fish intake and omega-3 fatty acids found in fish are other important dietary components linked with better cognitive health,<sup>48,49</sup> limited physical and economic access hinder optimal fish intake in SSA.<sup>50</sup>

There is a pressing need for comprehensive programs and policies that address the potential constraints of availability, cost, convenience, and preferences of healthy diets in LMICs. For example, in both urban and rural Indonesia, prevention strategies and public health messages in primary care facilities have been put in place to promote healthy diets containing tempe (a common Indonesian soyabean preparation) or tofu and fruits and provision of physical and psychosocial activities.<sup>32</sup> By adopting similar initiatives, LMICs can promote healthy dietary and activity patterns tailored to specific cultural backgrounds and geographical locations with the ultimate aim of reducing dementia risk and improving brain health.

## 2.2 | Physical activity

An increasing body of evidence underlines the importance of physical activity in dementia risk. Research in the U.S.-based Framingham Heart Study (FHS) cohorts shows that exercise may contribute to reduced risk of dementia and that sedentary individuals are at an increased risk of developing dementia compared to individuals with higher physical activity levels.<sup>51</sup> However, additional studies are needed to investigate the effects of physical activity on dementia risk in LMICs. A 2012 study of aging in Indonesia found that only 1.7% of older men and 0.7% of older women surveyed reported engaging in exercise or sports, with rates ranging from nearly 0% to 3.6% for women and 4.4% for

men across provinces.<sup>52</sup> Furthermore, significant regional differences show more older people in Jakarta engage in physical activity than in poorer regions such as Borobudur.<sup>32</sup> Research in Colombia has also shown that physical activity may substantially reduce the risk of MCI.<sup>53</sup> Public health strategies and interventions for enhancing overall health and reducing dementia risk in LMICs that focus on promoting physical activity may be best done via community centers in groups to ensure uptake and adherence.<sup>32</sup>

## 2.3 | Hypertension

Evidence from epidemiological studies suggests hypertension as a significant risk factor for dementia, especially midlife hypertension.<sup>54</sup> Promising results from clinical trials have also emerged, with the Systolic Blood Pressure Intervention Trial—Memory and Cognition in Decreased Hypertension study (SPRINT-MIND) showing that intensive blood pressure lowering reduces the composite outcome of MCI and probable dementia in those 50 and older.<sup>43,55,56</sup> From 1975 to 2015, the highest worldwide blood pressure values have been shown to be shifted from HICs to LMICs in South Asia and SSA.<sup>57</sup> Between 1990 and 2019, the summary exposure value (ie, a metric that captures risk-weighted exposure for a population or risk-weighted prevalence of an exposure) for high systolic blood pressure increased in SSA, the Middle East and North Africa, East Asia, and the Pacific. Despite this shift toward high blood pressure, only one in three individuals in LMICs are aware of their hypertension status, and only approximately 8% have their blood pressure under control.<sup>58</sup> A cross-sectional, pooled individual-level population-based study examining hypertension care in 44 LMICs found that countries in Latin America and the Caribbean performed better than predicted on hypertension care cascade defined based on having one's blood pressure measured, being diagnosed with hypertension, being treated for hypertension, and achieving control of one's hypertension. However, countries in SSA performed significantly worse on these steps relative to their predicted performance based on per-capita gross domestic product.<sup>59</sup> Thus, policies and interventions are urgently needed to increase hypertension awareness, diagnosis, control, and treatment rates in LMICs, as those efforts may contribute to not only increased cardiovascular health but also to improved brain health.<sup>58,60,61</sup>

## 2.4 | Social networks

Some studies suggest that supportive social networks may reduce the risk of AD and related dementias. Social networks may enhance cognitive resilience or the capacity for cognitive processes to be less impacted by age- or disease-related changes. A cross-sectional study evaluating 2171 U.S. adults revealed that social support in the form of supportive listening was associated with greater cognitive resilience, as indicated by individuals exhibiting higher levels of global cognitive function than predicted, given their cerebral volumes.<sup>62</sup> This is consistent with observational evidence indicating 30% to 50% lower

subsequent dementia risk is associated with greater social participation in midlife and late life.<sup>63</sup> Few studies have investigated the link between social networks and neurocognitive outcomes in LMICs. A recent study conducted in China, Ghana, India, Mexico, Russia, and South Africa among individuals aged  $\geq 50$  years found that every one-unit increase in the social participation score (a score ranging from 0 to 10, with higher scores corresponding to greater levels of social participation) was associated with a 13% decrease in the odds of developing MCI.<sup>64</sup> In Latin American countries such as Brazil and Columbia, social isolation or perception of loneliness was determined to be critical in predicting decline or performance in cognitive and functional abilities.<sup>33</sup> In studies from Indonesia, engaging in community activities has been associated with lower dementia risk.<sup>32</sup> Thus, psychosocial interventions and public health strategies aimed at increasing social support and participation may help reduce the risk of dementia, particularly in LMICs disproportionately affected by dementia.

## 2.5 | Sensory impairment: Prevention and intervention

Hearing and visual impairments are frequently underidentified among PLWD, but there is evidence to suggest that they are associated with accelerated cognitive decline, increased neuropsychiatric symptoms, and communication barriers.<sup>28,65</sup> Furthermore, sensory impairment reduces the quality of life for PLWD and their caregivers.<sup>66</sup> Recent longitudinal studies in older Americans have linked hearing aid use and cataract surgery with slower episodic memory decline than was observed before interventions.<sup>67</sup> More research is needed to determine whether early identification and treatment of sensory impairment in cognitively healthy individuals prevent neuropathology and reduce dementia risk (ie, selective primary prevention). Interventions for sensory impairment focused on indicated primary prevention or secondary dementia prevention (ie, preventing conversion from MCI to dementia and preventing the progression of existing dementia, respectively) are also lacking. There is clearly a need for appropriately powered hearing and vision impairment trials because scoping studies suggest consistent evidence is lacking for positive impact of hearing or vision interventions on cognitive function or decline, quality of life, or caregiver burden.<sup>66</sup> However, recently the Aging and Cognitive Health Evaluation in Elders (ACHIEVE) trial showed that hearing intervention in the Atherosclerosis Risk in Communities cohort might reduce cognitive change over 3 years in older adults (mean 79 years) at increased risk of cognitive decline but not in those at decreased risk of cognitive decline.<sup>68</sup>

To advance such efforts, the European **SENSE-Cog project** has developed multifaceted interventions to improve the lives of elderly individuals with sensory impairment and dementia. Preliminary results showed that the care dyads exhibited improved quality of life and sensory functional ability in a trial conducted in France, England, and Cyprus.<sup>69</sup> Findings from this project led researchers to develop the **SENSE-Cog project** in South Asia (Pakistan, India, and Bangladesh). All assessment and outcome rating tools were translated into local

languages, and intervention materials were modified to include culturally relevant pictures and consider participants' literacy levels. Preliminary findings from Pakistan demonstrated positive feasibility, acceptability, and tolerability of the intervention by study participants. However, study recruitment, timely hearing aid delivery, procedures for arranging home visits, and communication between referring clinicians and the study team were identified as areas in need of improvement.<sup>70</sup>

### 3 | VASCULAR COGNITIVE IMPAIRMENT, VASCULAR DEMENTIA, AND STROKE-RELATED COGNITIVE IMPAIRMENT

Vascular cognitive impairment (VCI) captures the entire spectrum of cognitive disorders related to cerebrovascular injury, ranging from mild to severe VCI, which is equated to VaD.<sup>71</sup> In HICs, VaD accounts for 15% of dementia cases, but the burden of VaD is even greater in LMICs, where it accounts for approximately 30% of dementias.<sup>20,21,72–74</sup> Consistent with this, the prevalence of cerebral small vessel disease causing VCI is also expectedly high in LMICs.<sup>75,76</sup> Research to elucidate effective preventive care or treatment strategies for VCI is limited in LMICs,<sup>43,77</sup> and more data are needed particularly from SSA, Eastern Europe, and Latin America.

The 2022 symposium devoted a session to VaD and stroke, covering a range of topics, including mild VCI or preclinical VaD and biomarkers of vascular contributions to dementia, stroke, and post-stroke dementia. In what follows, we provide the summary of key discussions from this session that were relevant to LMICs.

#### 3.1 | VCI and VaD

The prevalence of VCI is particularly high in India and in SSA countries such as Tanzania,<sup>74</sup> with nearly 40% of dementia cases attributed to VaD.<sup>77</sup> A hospital-based cohort of 42 patients in India with VaD found that subcortical dementia was the most common subtype of VaD (52%), followed by cortical–subcortical dementia (26%), strategic infarcts (14%), and cortical dementia (7%).<sup>78</sup> Furthermore, a large study of over 5000 individuals from nine Asian cities found that white matter lesions deemed to be of vascular origin on magnetic resonance imaging (MRI) or computed tomography (CT) are highly prevalent and are associated with worse cognitive performance.<sup>79</sup> *Post mortem* studies from Brazil have also identified a high prevalence of VaD. For example, a neuropathological examination of 1092 participants from the Biobank for Aging Studies in Brazil showed that cerebrovascular lesions are common, with 35% meeting the criteria for VaD diagnosis.<sup>21</sup>

Key risk factors for VCI are cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, smoking, obesity, atrial fibrillation, and coronary artery disease.<sup>71,80</sup> While these factors are prevalent in HICs, LMICs face a much greater disparity. For example, over three-quarters of cardiovascular deaths take place in LMICs,<sup>81</sup> yet the availability and affordability of cardiovascular and chronic disease

medications could be low in many LMICs relative to HICs.<sup>82</sup> In particular, hypertension is on the rise in LMICs, and many are not aware of their hypertension status.<sup>57,83</sup> Therefore, individuals in LMICs may be more susceptible to developing VCI and potentially more severe VaD.

#### 3.2 | Stroke and post-stroke dementia

Stroke is among the strongest predictors of VCI and VaD.<sup>80</sup> Furthermore, post-stroke dementia is recognized as a major subtype of VaD according to the Vascular Impairment of Cognition Classification Consensus Study classifications.<sup>84</sup> Between 1990 and 2019, the global stroke burden increased substantially, with the majority residing in LMICs.<sup>85</sup> The burden of stroke is especially high in Africa,<sup>76</sup> with an age-standardized incidence rate of up to 316 per 100,000 population and a prevalence rate of up to 1460 per 100,000 population.<sup>86,87</sup> In India, distinct patterns of ischemic stroke subtypes have been reported, with intracranial atherosclerosis accounting for 30% of ischemic strokes.<sup>88</sup> While the prevalence of stroke is higher in LMICs compared to HICs,<sup>89,90</sup> there are limited data on the prevalence of post-stroke dementia in LMICs. Studies in SSA have reported varying prevalence estimates for post-stroke cognitive impairment, ranging from 6.3% in Nigeria to 25% in Central Africa.<sup>91</sup> The Cognitive Function After STroke (CogFAST) Nigeria Study found that at 3 months after stroke, 40% of participants had cognitive impairment with no dementia, and 8.4% had dementia.<sup>92</sup> Important determinants of cognitive impairment after stroke in the CogFAST study were increasing age, lower education, pre-stroke cognitive decline, medial temporal lobe atrophy, and pre-stroke diet.<sup>92</sup>

Collectively, severe VCI or VaD and stroke continue to represent a significant burden in LMICs compared to HICs, and this gap is increasing. Early identification and effective management of cardiovascular risk factors and diseases in LMICs is a crucial step in alleviating the burden of stroke and VaD, which are on the rise in LMICs. To further enhance VaD research and its robust impact in LMICs, sustainable equitable partnerships must be built. In LMICs, several promising future research directions are emerging to address the challenges of VaD in the region. These studies aim to conduct longitudinal studies on larger samples, establish molecular and genetic risk prediction tools for VCI, understand neuroimaging and electroencephalogram determinants of VaD, and elucidate cardiovascular risk factors and cognitive outcomes that lead to VaD.

### 4 | COGNITIVE DYSFUNCTION IN PARKINSON'S DISEASE

The 2022 symposium included a session on movement disorders with a discussion on mechanisms and genetic factors that may underlie the link between movement disorders and cognitive impairment with a particular focus on Parkinson's disease (PD). Cognitive impairment is the most common non-motor symptom (NMS) of PD, ranging from mild cognitive difficulties in one or more of the cognitive domains to

severe dementia.<sup>93</sup> The prevalence of MCI in PD has been estimated to be 40%.<sup>94</sup> Furthermore, individuals with PD are five to six times more likely to develop dementia, and this risk increases with age and PD symptom severity.<sup>95</sup> While the WHO has identified LMICs as the region with the most affected PD individuals,<sup>96</sup> there is a significant lack of data on the burden of PD-associated cognitive impairment in LMICs, including Asia and Latin America.

Research on PD-associated cognitive impairment within Africa was particularly highlighted in the discussions held at the symposium. It was noted that there is a lack of studies on the prevalence and burden of PD-associated cognitive impairment in Africa, with most studies being hospital-based. One of the earliest reports in Africa was from a hospital-based study by Akinyemi et al.<sup>97</sup> This study determined the frequency, pattern, and predictors of cognitive impairment among 51 Nigerian PD patients that showed the rate of cognitive impairment in PD patients was 21.6% versus 4% in controls, with memory, language, and executive function being most affected.<sup>97</sup> Furthermore, older age at PD onset was the only independent predictor of cognitive impairment.<sup>97</sup> Another Nigerian study assessing the frequency of cognitive impairment and depression among 40 PD patients reported that 60% of PD patients had cognitive impairment compared to 5% in controls.<sup>98</sup> A more recent study assessing the profile and burden of NMS within 825 members of the Nigeria Parkinson Disease Registry reported that frequencies of cognitive complaints ranged between 27% and 46%.<sup>99</sup> Collectively, these data suggest that cognitive impairment is highly prevalent in the African PD population and similar to that in other populations.<sup>99</sup>

Epidemiological data on PD-associated cognitive impairment are still lacking in LMICs. There is an especially urgent need for robust estimates of prevalence, incidence, and risk factors from population-based studies to better evaluate the burden of PD-associated cognitive impairment in diverse populations. Furthermore, developing cross-culturally validated and efficiently implementing cognitive screens for PD in LMICs is essential. It is especially important since cognitive impairment in PD is associated with a loss of independence, worsening quality of life, increased caregiver burden, and higher mortality risk.<sup>100</sup> Finally, unequal healthcare access, lack of resources, and treatment for people living with PD and associated neurocognitive outcomes need to be addressed in LMICs.

## 5 | HUMAN IMMUNODEFICIENCY VIRUS AND DEMENTIA

In the era of antiretroviral therapy (ART), human immunodeficiency virus (HIV) has emerged as a lifelong chronic disease that carries several HIV-related complications. One of the major HIV-related complications is cognitive impairment,<sup>101</sup> which diminishes the health-related quality of life in people living with HIV (PLWH).<sup>102</sup> HIV-associated neurocognitive disorder (HAND)<sup>103</sup> has an estimated global prevalence of 43%, with South America and SSA being most affected.<sup>104</sup> A systematic review in 2021 found that prevalence estimates for HAND in SSA varied between 14% and 88% and were impacted by factors like different diagnostic approaches, sampling

methods, and ART status.<sup>105</sup> Another systematic review of 50 studies from 15 SSA countries showed that the prevalence of symptomatic HAND among PLWH aged  $\geq 50$  years on cART ranged between 19% and 61%.<sup>106</sup> Furthermore, individuals growing old on ART may be susceptible to more cognitive decline as a result of the disease if not treated early as well as the possible effects of long-term ART use on the brain. However, further research needs to be conducted on individuals surviving into old age with HIV.

### 5.1 | Variations in prevalence of HAND

Variable prevalence estimates for HAND in LMICs may stem from differences in diagnostic approaches and neuropsychological tests. In a 2021 study, researchers applied 20 different methods for determining cognitive impairment in 148 South African PLWH who also underwent structural MRI and diffusion tensor imaging. Researchers observed wide variation (20% to 97%) in estimated rates of cognitive impairment defined by each method, while no method correlated with neuroimaging markers of HIV-associated brain injury.<sup>107</sup> Other factors that may contribute to variable prevalence estimates of HAND are psychosocial and educational factors. A study conducted in South Africa in 2013 found that HIV status and education were the strongest predictors of total scores on the Montreal Cognitive Assessment (MoCA).<sup>108</sup> Another study in South Africa found that psychosocial factors (ie, less education and greater food insecurity) were stronger predictors of poorer overall cognitive performance than medical factors among PLWH.<sup>109</sup> Therefore, applying solely quantitative methods based purely on cognitive test scores to diagnose cognitive impairment in PLWH may not accurately reflect HIV-associated brain injury. Incorporating clinical judgment and factors that affect performance on neuropsychological tests are important considerations that can enable improved assessment and diagnostic accuracy of cognitive impairment in PLWH.<sup>107,109</sup>

Currently, criteria for HAND can be met based on cognitive tests alone, and many researchers have argued that this approach is inappropriate.<sup>110,111</sup> In addition, some studies have cautioned on potentially high false positive classification rates for HAND.<sup>112</sup> Thus, clinicians and policymakers should exercise appropriate caution when interpreting research findings on HAND burden. While underestimating the prevalence of cognitive impairment in PLWH will negatively impact the speed at which it can be contained, overestimating the prevalence may lead to misallocating resources that are especially scarce in LMICs.<sup>105</sup> Overestimating cognitive impairment may also increase the risk of stigma and discrimination toward PLWH.<sup>110,113</sup>

To improve HAND diagnostic criteria, researchers and clinicians from neurology, psychiatry, and infectious disease developed an International HIV-Cognition Working Group, with approximately 50% LMIC membership. The working group has published recommendations for evaluating neuropathology, interpreting cognitive test results, and diagnosing cognitive impairment in PLWH.<sup>111</sup> The group has proposed the conceptual separation of HIV-associated brain injury from other causes of brain injury in PLWH. It has also recommended moving away from only quantitative methods of diagnosing cognitive impairment in



PLWH while placing emphasis on the clinical context. These recommendations will require validation, field testing, and a broader consensus but may lead to the development of a more precise phenotype for cognitive impairment in PLWH.<sup>111</sup>

## 6 | LANGUAGE, APHASIA, AND DEMENTIA

Traits of dementia-related speech and language deficits, such as aphasia and subtypes such as dysnomia, characterized by difficulty in finding and recalling words, are valuable early indicators of cognitive impairment.<sup>114,115</sup> However, research and clinical criteria have largely been limited to Western languages and have not adequately accounted for the impact of linguistic diversity on the manifestation of aphasia. Before 1945, most research on aphasia was conducted in German and French, with subsequent studies primarily conducted in English.<sup>116</sup> A study of 1265 articles on aphasia published between 2000 and 2009 reported a pronounced bias toward articles focused on English-speaking patients, accounting for 62% of all papers.<sup>116</sup> In comparison, some of the most widely spoken languages in the world (eg, Arabic, Hindi, Bengali, Russian, and Portuguese) accounted for only <0.5% of the aphasia literature. More than 90% of aphasia treatment studies were based on English, German, and Dutch-speaking patients.<sup>116</sup> Such findings underscore the extreme bias toward Western languages in aphasia or dysnomia<sup>117</sup> assessment and treatment, limiting clinical findings' applicability and generalizability to diverse populations.

### 6.1 | Heterogeneity in aphasia manifestation

It is important to note that aphasias manifest heterogeneously across different languages. In a study of linguistic impairment patterns in Bengali speakers, Bengali-speaking AD participants tended to significantly underuse pronouns, whereas English-speaking AD patients tended to overuse them.<sup>118</sup> Other studies have shown that German-<sup>119</sup> and Hebrew-speaking AD patients<sup>120</sup> exhibited no impairment in verb inflection, whereas English-speaking AD patients tended to have more inflectional errors than the respective control patients.<sup>121</sup> It has been suggested that reference to the past is challenging for patients with agrammatic aphasia, but a study of time reference in Thai speakers with agrammatic aphasia showed inconsistent results.<sup>122</sup> Thai agrammatic speakers had more vulnerability to future reference than the present and the past.<sup>122</sup> Thus, the morphology and characteristics of a patient's language are important considerations for the accurate assessment, diagnosis, and treatment of aphasia. Future studies are essential to enhance our understanding of cross-linguistic differences in aphasia, particularly across morphologically distinct and underexplored languages.

Language-specific considerations should be made for bilingual and multilingual patients. Most bilingual aphasias manifest in parallel in both languages, but there is also evidence of differential or selective aphasia.<sup>123</sup> For example, some studies show that in bilingual patients with aphasia, the first language is best preserved,<sup>124</sup> while others show

that the last language is best preserved.<sup>123</sup> Older studies also suggest that the emotionally relevant language may be better preserved, or bilingual patients may exhibit different types of aphasias in different languages.<sup>123,125</sup> In bilingual patients with semantic dementia, the less proficient language was lost at presentation, with some patients even failing to recognize the language. This was seen across English and several Indian languages like Kannada, Hindi, Tamil, and Telugu.<sup>126</sup> In bilingual agrammatic speakers of Swahili and English in Africa, agrammatic patients make no errors in the past or future tense in Swahili. At the same time, they have selective deficits in producing past tense in English.<sup>127</sup> Such observations have relevant implications for assessing aphasia in multilingual patients in LMICs. This also implies aphasia treatments may not be generalizable to various linguistic and cultural backgrounds.

### 6.2 | Effect of dual language use on cognition

It is also important to note that dual language use may affect cognitive function. In this regard, there are two main competing hypotheses: (1) the subtractive effect of bilingualism where bilinguals show deficiencies in neuropsychological test performance, particularly naming and verbal fluency tests, compared to monolinguals and (2) the additive effect of bilingualism where bilinguals may outperform monolinguals in tasks involving executive controls, particularly tasks requiring inhibitory control in non-verbal tasks.<sup>128-130</sup> The benefit of bilingualism has also been shown in verbal memory tests in which inhibitory control is required to reduce proactive and retroactive interference.<sup>131</sup> The advantage of bilinguals in tasks requiring inhibitory control may be the consequence of bilinguals inhibiting the language not in use at any given moment<sup>132</sup> or their constant need to keep track of both languages in order to select and activate the appropriate language (switching).<sup>128,130,133</sup> It has also been shown that keeping two languages active increases cognitive reserve and may delay the emergence of dementia.<sup>128,134</sup> Furthermore, bilingualism has been associated with structural and functional alterations in the brain.<sup>135-137</sup> Further research is needed to better understand how bilingualism is related to neurocognitive processes though, as some studies have failed to replicate empirical evidence of the protective effect of bilingualism on dementia progression.<sup>138-140</sup>

In summary, to enhance our understanding of aphasia across languages and cultures, it is important to develop culturally sensitive assessment tools and appropriately tailored interventions. Neglecting cultural and linguistic diversity, as well as multilingualism in aphasia, may lead to incorrect diagnosis and ineffective treatment strategies. Such oversight could lead to inappropriate or inaccurate theories that cannot be generalized to diverse populations.

## 7 | GENETICS OF DEMENTIA

Profound insights into the genetics of AD have been gained from focusing on genes that cause autosomal dominant familial AD (FAD), as well

as genes that have a substantial influence on late-onset AD (LOAD), such as APOE.<sup>141</sup> Building on this foundation, more recent research has identified additional genetic variants that modify AD risk.<sup>142,143</sup> Historically, most research on the genetic risk of AD focused on populations with Caucasian European backgrounds.<sup>144</sup> However, more recent studies in LMICs and other global population groups highlight the importance of diversity and inclusion of all populations in genetic research because many genetic variants that influence AD risk are not present in European local ancestry but instead reflect genetic admixtures derived from European, African, Amerindian, and East Asian ancestries.<sup>145</sup> This more recent inclusion of diverse global populations contributes to tremendous advances in unraveling the variation and complexity of genetic risk and resilience to AD and related dementias.<sup>146</sup>

## 7.1 | Autosomal dominant familial AD in Latin America

Studies of geographically and genetically isolated populations in Antioquia Colombia have led to the exciting understanding of a form of FAD caused by an E280A point mutation in the presenilin 1 gene (*PSEN1*).<sup>147</sup> Following the identification of the first cluster family in the 1980s, subsequent pedigree identification, genealogy, and follow-up work throughout rural Antioquia identified 25 affected families sharing a common ancestry that could be traced back to a founder in the 18th century.<sup>148</sup> This cohort now consists of 25 multigenerational families and includes around 5000 individuals and about 1200 living *PSEN1* E280A mutation carriers.<sup>149</sup>

Collaborative studies on this Colombian kindred have established key characteristics of AD neurocognitive and neuropathological progression in *PSEN1* E280A carriers. Neuropsychological testing identified several stages of progressive clinical deterioration that can take as long as 25 years, including asymptomatic pre-MCI, symptomatic pre-MCI, MCI, and dementia with overall clinical deterioration.<sup>150,151</sup> Positron emission tomography (PET) imaging of *PSEN1* E280A carrier brains found fibrillar A $\beta$  accumulation beginning during asymptomatic stages at a mean age of approximately 28 years.<sup>152</sup> On the other hand, elevated levels of tau deposition were observed 6 years before AD clinical onset, at the mean age of 38 years, suggesting a decade gap between the development of amyloid and tau-PET pathology.<sup>153</sup> In addition, *PSEN1* E280A carriers have low levels of cerebrospinal fluid (CSF) A $\beta$ 1-42<sup>154</sup> and high levels of plasma tau phosphorylated at threonine 217 (p-tau217) and neurofilament light (NfL) up to 20 years before the first symptoms of MCI.<sup>155</sup> *Post mortem* studies also showed a high degree of cerebral small vessel disease pathology in *PSEN1* E280A carriers in Colombia, suggesting covert vascular pathology in *PSEN1* that is not directly associated with brain deposition of amyloid.<sup>156</sup> This identification of AD biomarkers many years before clinical symptoms and the association of biomarkers with clinical phases of AD progression has important implications for early AD diagnosis and the evaluation of disease-modifying AD therapies in clinical trials.

Delayed dementia onset beyond one standard deviation from the average is associated with decreased cortical tau pathology and increased activity of the proteasome system, without any modification of A $\beta$ -associated pathology.<sup>157</sup> Interestingly, resistance to early-onset FAD conferred by the rare APOE  $\epsilon$ 3/ $\epsilon$ 3 Christchurch R136S mutation was discovered in a *PSEN1* E280A carrier who did not develop MCI until her 70s.<sup>158</sup> Brain imaging and autopsy revealed low levels of tau pathology and neurodegeneration in key cortical areas, despite a high A $\beta$  plaque burden.<sup>159</sup> This suggests a role of APOE3 Christchurch variant in the clinical presentation, age of onset, and biomarker progression in autosomal-dominant AD. More recently, another case was identified who, despite carrying the E280A mutation, remained cognitively intact until 67 years of age since this individual also carried a heterozygous rare variant of the Reelin gene. This remarkable protection was associated not with the profile or severity of AD pathology but with increased neuronal density in the entorhinal cortex.<sup>160</sup> Finally, Colombian individuals with AD or related dementias carrying additional *PSEN1* pathogenic variants that cause early-onset FAD, as well as multiple rare variants, develop other forms of autosomal-dominant early-onset dementia.<sup>145</sup>

Together, these studies underscore the genetic insights that can be gained from studies that include an admixture of genetic alleles from multiple ancestries and reinforce the need to include diverse populations for gene-trait association studies. The discovery of additional genes in diverse populations is critical to filling knowledge gaps in the functional genomic landscape of AD pathogenesis, such as explaining clinical observations and providing clues to potential novel disease-modifying therapies. It is expected that the Recruitment and Retention of Alzheimer's Disease Diversity Genetic Cohorts in the AD sequencing project (READD-ADSP) will hold great potential for finding new variants in LMICs, as well as nine SSA countries involved in the African Dementia Consortium<sup>161</sup> and the Multipartner Consortium to expand the genetics of dementia research in Latin America (ReDLat).<sup>146</sup>

## 7.2 | Effects of APOE on AD risk across diverse populations

APOE is the strongest genetic risk factor for LOAD, with three isoforms –  $\epsilon$ 2,  $\epsilon$ 3, and  $\epsilon$ 4 – that differentially influence AD risk.<sup>162</sup> Although the initial studies of cohorts with European ancestry suggested that APOE  $\epsilon$ 4 homozygotes had a substantially higher AD risk than APOE  $\epsilon$ 3 homozygotes,<sup>163</sup> subsequent research has found that the risk of developing AD in the presence of the APOE  $\epsilon$ 4 allele varies across populations with diverse ancestral backgrounds.<sup>23,164–166</sup> It has been shown that the strongest risk of AD from the APOE  $\epsilon$ 4 allele is in East Asians, followed by non-Hispanic Whites, and considerably lower risk in African-ancestry populations such as Nigerian and East Africans and African Americans.<sup>20,22,164,165,167,168</sup> Interestingly, ancestry analysis showed that the differential risk of AD from APOE  $\epsilon$ 4 between populations and individuals is due to differences in the local ancestry surrounding the APOE gene rather than differences in global ancestry. Specifically, when the APOE  $\epsilon$ 4 allele is present on a haplotype

originating from African ancestry, the risk of AD is substantially lower than on a haplotype originating from European ancestry.<sup>22,169</sup>

Genetic interaction studies to identify and characterize the protective variant in the African local ancestry around *APOE* showed that a protective locus lay approximately two megabases (mB) upstream of the *APOE* locus and reduced the risk effect of *APOE*  $\epsilon$ 4 homozygotes in African local ancestry by 75%. However, this protective allele is only in 11% of the African ancestry population and very rare in others. Thus, while it contributes to lowering the risk for AD from *APOE*, other factors are important.<sup>165</sup> Single-nucleus RNA sequencing of the frontal cortex of homozygous *APOE*  $\epsilon$ 4 AD patients revealed that the *APOE* gene was differentially expressed between individuals with African or European local ancestry, with higher levels in European local ancestry frontal cortex, particularly in astrocytes and microglia.<sup>170</sup>

These studies and related research highlight the differences in the genetic contributions to AD across various ancestries. Future studies focused on diverse populations are essential as they can provide valuable insights into AD pathology that may not be available when studying single populations. By identifying protective factors for AD, such as *APOE*  $\epsilon$ 4 in African-Ancestry populations, we can move forward with AD therapeutics efforts that cater to the needs of all populations.

## 8 | COGNITIVE TESTING AND DIAGNOSIS

### 8.1 | Delays and underdiagnosis of dementia in LMICs

There is a critical need for early and accurate diagnosis of AD to ensure that eligible individuals receive treatments at the earliest time possible.<sup>171,172</sup> Furthermore, early dementia diagnosis can provide patients and families the opportunity to begin long-term legal, financial, and care planning. However, 75% of dementia cases worldwide and 90% in LMICs go undiagnosed.<sup>173</sup> Low availability of biomarkers in LMICs contributes to this discrepancy, as discussed in more detail in section 9.

Barriers to timely diagnosis of dementia, including cultural trends, exist at multiple levels. Patients and family members may have limited awareness of dementia, attribute their symptoms to normal aging, or experience feelings of shame and fear. In addition, clinicians may lack the necessary training, enough time, and cognitive tools to assess dementia patients.<sup>174</sup> Only recently have there been efforts to assess which cognitive tests are best to use in LMICs, and particularly in people with low education, to identify cognitive deficits.<sup>175</sup>

At a higher level, health systems with poor infrastructure and too few resources may impede early dementia diagnosis.<sup>176</sup> In HICs, racial and ethnic disparities in the timeliness and breadth of dementia diagnosis have also been reported. For example, one study found that, compared with White Medicare beneficiaries in California, those who identified as Asian, Black, or Hispanic were less likely to receive a timely dementia diagnosis.<sup>177</sup> In LMICs across Latin America, the combination of different barriers and socioeconomic disparities strongly impacts underdiagnosis.<sup>178,179</sup> Intriguingly, Asian beneficiaries also received

fewer diagnostic evaluation elements.<sup>177</sup> A study in Bangalore showed that among 855 total patients with dementia, the median time from symptom onset to diagnosis (TTD) was 2 years. Among patients with young onset dementia, the median TTD was 3 years. In addition, patients with VaD were diagnosed significantly earlier following symptom onset than patients with AD or frontotemporal dementia (FTD). These findings indicate substantial delays in the diagnosis of dementia in urban India that are likely exacerbated in rural and lower educated regions.<sup>180</sup>

### 8.2 | Cross-cultural adaptation and validation of cognitive testing

Effective neuropsychological tests applicable across varied cultures are important in the assessment of cognitive function. While several effective neuropsychological tools are widely available for use in HICs, this is not the case for most LMICs.<sup>181</sup> In India, it has been necessary to develop various neuropsychological batteries for use in older persons, especially within the rural, low-educated elderly population.<sup>182,183</sup> In Indonesia use of different screening test may be responsible for very high estimates of dementia (up to 33%) and standardization and validation of screening tests is important for accurate estimates.<sup>32</sup> To reduce disparities in dementia diagnosis, neuropsychological tools, and resources must be adapted and validated for use in LMICs.

Researchers have begun validating and culturally adapting the Eight-Item Informant Interview to Differentiate Aging and Dementia (AD-8) for use in Ethiopia<sup>184</sup>; Alzheimer Disease Centers' Neuropsychological Test Battery in the Uniform Data Set (UDS-III), Tablet-based brain health assessment (BHA), and Pfeffer Functional Activities Questionnaire (PFAQ) for use in Botswana (unpublished data) and a brief version of the Addenbrooke Cognitive Examination (ACE) for use in Brazil.<sup>185,186</sup> Several cognitive tests have also been cross-culturally adapted and standardized for use in Latin America and Africa.<sup>187–193</sup> These efforts involve forward- and back-translating tools into target languages, conducting cognitive interviews to assess respondents' interpretations of test questions, collecting feedback from expert panels on test language and cultural appropriateness, and performing statistical analyses to isolate the questions with the highest predictive power for identifying cognitive impairment.<sup>181,184,186,194</sup> In India, it has been shown that there is also utility in modifying verbal-language/orientation-memory (VLOM) ratios from the ACE battery for early identification and clinical differentiation of AD from other forms of dementia.<sup>195,196</sup>

To improve dementia detection in under-resourced areas lacking comprehensive neuropsychological testing, validation and cultural adaptation efforts, including the need to cater to multiple languages for cognitive screening tools, are needed in more LMICs.<sup>197</sup> Future efforts should consider how an individual's performance on a cognitive test may be impacted by their culture, acculturation, degree of bilingualism, and both quality and level of education and socioeconomic inequality, which can include unfamiliarity with – and fear of – test-based assessments.<sup>198</sup>

## 9 | BIOMARKERS AND BIOBANKING

### 9.1 | Biomarkers

Various biomarkers for dementia have been developed that not only provide valuable insight into disease pathology but also pave the way for more efficient risk stratification, diagnosis, and monitoring in the context of therapeutic and preventive interventions. This includes neuroimaging biomarkers of protein deposition, as well as structural and functional alterations (eg, structural and functional MRI, amyloid and tau PET) and fluid biomarkers (ie, CSF and blood-based biomarkers).<sup>171</sup> However, MRI and PET are not widely available in most LMICs, and current knowledge on dementia biomarkers is derived mostly from studies of White individuals.

Recently, blood-based biomarkers of AD have been shown to significantly improve the diagnostic accuracy of AD by providing less invasive, more feasible, and more cost-effective approaches compared to PET neuroimaging and CSF analysis.<sup>199</sup> In the United States, evidence from diverse ethnic and racial groups has been lacking, though recent studies have included African American and Hispanic participants. However, compared to studies on non-Hispanic White individuals, the numbers remain small. Systematic review and meta-analysis found that only five studies compared AD fluid biomarkers between African American or Black Africans and White individuals.<sup>23,200</sup> Meta-analyses of these studies showed that CSF total tau (t-tau) and p-tau181 levels were consistently lower in African Americans than in White individuals with normal cognition and MCI. Such findings underscore the importance of considering ethnic and racial factors that may influence AD biomarker levels.<sup>201</sup> Regionally oriented frameworks can help to develop more effective and feasible biomarkers in LMICs and other low-resource-setting regions. Improved sampling protocols, for example, through finger prick testing with no need for centrifugation and storage at room temperature, are now emerging, which should facilitate biomarker studies in remote or low-resource settings.<sup>202</sup>

### 9.2 | Biobanks

Brain banks are essential for the study of brain aging and neurodegenerative disorders, particularly AD.<sup>203</sup> While the majority of PLWD reside in LMICs, most brain banks are in HICs. Establishing biobanks in LMICs is difficult due to a lack of institutional funds and external stakeholder support, including poor willingness toward brain donation. However, biobanking in LMICs can provide valuable insights into disease pathology within the context of diverse ancestry/geographical backgrounds.<sup>204–207</sup>

In Africa, the Ibadan Brain Ageing, Dementia And Neurodegeneration (IBADAN) brain bank and the African Neurobiobank ELSI Project<sup>205,208</sup> have demonstrated that 19% to 27% of older Africans are willing to donate brains for research and have also drawn attention to the necessity of paying attention to the legal issues related to biobanking in a unique African context.<sup>206,209,210</sup> The Biobank for Aging Studies (BAS) in Sao Paulo, Brazil<sup>204</sup> has shown that 22% of cases

with a Clinical Dementia Rating (CDR) score of zero met the criteria for a neuropathological disease diagnosis, with AD being the most common.<sup>21</sup> It has also been shown that VaD and cerebral small vessel disease are higher in Brazil than in other clinicopathological studies.<sup>211</sup> Data from the BAS further demonstrated that African ancestry may be highly protective against AD by showing a negative correlation between African ancestry and neuritic plaques.<sup>200</sup> Additionally, it has been shown that the APOE  $\epsilon$ 4 genotype has different effects on AD pathology and clinical features, depending on the patient's genetic lineage. It was shown that APOE  $\epsilon$ 4 carriers with high African ancestry proportion and worse functional cognitive scores were not affected as they would be in Europeans.<sup>165</sup>

These results demonstrate the need for localized study of AD and dementia biomarkers in LMICs, as geography-dependent factors such as ancestry can have significant impacts on the disease. The scarcity of brain banks in LMICs is further illustrated in Latin America and the Caribbean region. Besides the Brazilian BAS, currently only four other functioning biobanks are preserving and collecting brain tissue: Argentina, Colombia, Mexico, and Dominican Republic. More often than not, brain banks in this region are associated with specific research programs and populations, such as the brain bank in Medellin, Colombia. On the other hand, Sri Lanka's NeuroBioBank may provide a model for establishing biobanks in low-resource settings. With funding from the National Institutes of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS), this biobank has collected biological samples from 500 healthy controls and roughly 2000 patients with brain diseases. It has also established mobile clinics across Sri Lanka and conducted genetic tests to assess genetic traits and risk factors for rare neurodegenerative diseases.<sup>212</sup> Notably, researchers found that 285 patients tested negative for known mutations associated with neurodegeneration, indicating novel mutations may remain available for discovery. This presents opportunities for companies in the biomedical industry to collaborate with biobanks, to enable resource sharing and aid in new mutation discovery and gene therapy development.<sup>213</sup>

## 10 | DEMENTIA CARE AND POLICY

The 2022 symposium also devoted a session on dementia care and policy to a discussion of challenges and best practices for dementia care in LMICs. The session highlighted that the most effective strategies for dementia policy in LMICs were those that are culturally appropriate and meaningful to the communities that are impacted by neurocognitive illnesses. In particular, lack of institutional funding, stigma toward dementia, and low education on the causes of dementia and AD were highlighted as leading causes of poorer dementia diagnostic and treatment outcomes in SSA and other LMICs.<sup>174,214,215</sup>

To broaden the scope of dementia research in LMICs and build evidence on dementia care and services, the Strengthening Responses to Dementia in Developing Countries project (STRIDE, [www.stride-dementia.org/](http://www.stride-dementia.org/)) was launched in seven LMICs comprising Brazil, Indonesia, India, Jamaica, Kenya, Mexico, and South Africa.<sup>216</sup>

**TABLE 1** Recommendations of Nairobi Declaration 2022 on dementia impact.<sup>220</sup>

Rethink global approach to dementia by focusing on underserved and underrepresented populations.
Increase investments in LMICs to address challenges and seize opportunities related to various dementia subtypes.
Implement and evaluate population-level risk reduction strategies by engaging policymakers and advocacy organizations.
Consider nutritional and psychosocial factors for promoting brain health, in addition to improving education and cardiovascular health.
Equip health and social care services with necessary resources in LMICs as well as in low-resourced HICs to meet the needs of the aging population.
Support research into more pragmatic, affordable, and effective solutions.
Train highly motivated early career researchers (ECRs) in higher education institutions in both HICs and LMICs.
Promote research in LMICs by establishing a research framework with international collaboration and prevent the brain drain from LMICs.

STRiDE Kenya launched a dementia anti-stigma intervention in rural communities that have a poorer understanding of the condition. The intervention educated communities about dementia symptoms, addressed myths and misconceptions about dementia, showed the impact of discrimination and human rights violations against PLWD, and encouraged social inclusion of people living with dementia. One month after the intervention, STRiDE Kenya reported that participants were less likely to believe that doctors should force treatment on unwilling patients and more likely to believe that greater spending on dementia care is a useful investment. Furthermore, an ongoing study entitled "Integration and evaluation of a community-level dementia screening program in Kenya (DEM-SKY)"<sup>217</sup> has begun working to normalize dementia in Africa by targeting 2400 older persons aged 60 and older. This project aims to increase timely and accurate dementia detection using evidence-based tools, improve access to quality dementia care, prioritize dementia in policy-level discussions, and increase funding for dementia care and research.

Jamaica and other Caribbean countries face significant impacts associated with dementia care, where the current costs of informal care outweigh costs in the public sector. This means considerable intervention is needed to prepare health and social care systems to care for people with dementia. Underpinned by a theory of change adapted by the STRiDE Jamaica team and over 50 representatives from multiple sectors, researchers prioritized a knowledge exchange approach to creating services to increase formal care and reduce the impact on informal caregivers. With the funding and resource support from the research grant, the local team focused on building greater coordination among private- and public-sector stakeholders to make further progress on state support for medication subsidization, formal care, and support for caregivers. STRiDE Jamaica also provided formal caregivers with trainings via webinars and conferences on how to appropriately manage dementia. Informal caregivers, that is, family and community-based caregivers, were likewise provided with training to develop skills in care activities, such as stimulating activities, as well as daily living tasks, including shopping, preparing food, and transportation.<sup>218</sup>

## 11 | CONCLUSIONS

Dementia has become an escalating challenge for public health, society, and the economy in LMICs, with multiple factors at play. Such factors

include a high prevalence of risk factors, poor dementia awareness, stigma and misconception surrounding dementia, inequitable access to healthcare resources, and socioeconomic disparities. Therefore, a multifaceted approach is necessary to reduce the impact of dementia in LMICs. Developing national dementia plans and implementing robust policies focused on enhancing dementia care infrastructure and services are crucial. Furthermore, national and international collaborations that lead to sharing knowledge and resources are key factors. By ensuring the inclusion of individuals from LMICs in research studies and pharmacological (and non-pharmacological) clinical trials (Figure 2) and building research capacity in these regions,<sup>219</sup> we can benefit from more effective preventive and treatment strategies for dementia.

In conclusion, we would like to echo the recommendations of the Nairobi Declaration made at the 2022 Symposium on Dementia and Brain Aging in LMICs to call upon the global community to take the previously mentioned actions to improve dementia prevalence, outcomes, and personal and societal impacts in LMICs<sup>220</sup> (Table 1).

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from RUD Instrument paid to European Health Economics; a consulting fee paid to European Health Economics from H. Lundbeck A/S; personal fees from Eli Lilly Inc. for lectures, presentations, speakers bureaus, manuscript writing, or educational events; and support from Bioarctic AB for attending meetings and/or travel. J.H.L., in the past 36 months, reports serving on the external advisory board for the Alzheimer's Disease Resource Center for Minority Aging Research, School of Medicine, University of Texas, Rio Grande Valley (UTRGV), and for the Center for Life Sciences, Nazarbayev University, Astana, Kazakhstan. I.L., in the past 36 months, reports receiving payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from the advisory board - Novo Nordisk; support from Roche for attending AAIC (November 2022); and serving as director, Lewy Body Ireland (charity). G.L. reports receiving support to attend the meeting presented in this paper. B.L.M., in the past 36 months, reports receiving payments for royalties or licenses from Cambridge University Press, Elsevier, Inc., Guilford Publications, Inc., Johns Hopkins Press, and Oxford University and Taylor & Francis Group; consulting fees from Massachusetts General Hospital Alzheimer's Disease Research Center (ADRC) Scientific Advisory Board (SAB) (2021, 2022, and 2023), Stanford University ADRC SAB (2021, 2022, and 2023), University of Washington ADRC SAB (2021, 2022, and 2023), and Genworth Medical Advisory Board (March 2023); payments for lectures, presentations, speakers bureaus, manuscript writing, or educational events from the Institute for Lifelong Learning (May 2023), Global Summit on Neurodegenerative Diseases (June 2021), Korean Dementia Society (July 2022), Massachusetts General Hospital, dementia course (2022 and 2023), National MS Society, Don Paty Lectureship (June 2021), Ochsner Neuroscience Institute (November 2021), Providence Saint Joseph Medical Center (September 2021), Taipei Medical University, Dementia Center (March 2022), UC Irvine Institute for Memory Impairments and Neurological Disorders (UCI MIND) (March 2022), University of California, Los Angeles (UCLA) Grand Rounds (April 2022), and University of Texas, Center for Brain Health (January 2021). In addition, B.L.M., in the past 36 months, reports receiving travel and lodging support from the Association for Frontotemporal Degeneration (AFTD) Education Symposium, St. Louis, MO (May 2023), Milken Institute FTD Scientific Retreat, Los Angeles, California (March 2023), California Institute of the Arts, Los Angeles, California (April 2022), and UCLA; serving as external, scientific, or medical advisor for Arizona Alzheimer's Consortium, Association for Frontotemporal Degeneration, Buck Institute for Research on Aging Scientific Advisor Cure ALS, John Douglas French Alzheimer's Foundation, Fundación Centro de Investigación Enfermedades Neurológicas, Madrid, Spain, Genworth, The Larry L. Hillblom Foundation, Massachusetts General Hospital ADRC, National Institute for Health Research Cambridge Biomedical Research Center and its subunit, the Biomedical Research Unit in Dementia, Stanford University ADRC, University of Southern California P01 Urban Air Pollution and Alzheimer's Disease: Risk, Heterogeneity, and Mechanisms, University of Washington ADRC; serving as Director and Internal Advisor for The Bluefield Project to Cure FTD; serving as Founding Director for Global Brain Health Institute; serving as Affiliated Faculty with Institute for Neurodegenerative Diseases;

and serving as Co-Director and Scientific Advisor for the Tau Consortium of the Rainwater Charitable Foundation. N.N., in the past 36 months, reports having a leadership or fiduciary role in the Uganda Society for Health Scientists and serving on a Data Safety Monitoring Board or Advisory Board of Washington University, St. Louis, MO, USA. S. Nightingale, in the past 36 months, reports travel expenses to attend HIV CNS Day 2022 and Naples NeuroHIV conference 2023. G.N. reports receiving travel and accommodation support from the organizing committee of the Dementia and Brain Aging in Low- and Middle-Income Countries Conference in 2022. M.O.O., in the past 36 months, reports receiving payment for attending the Alzheimer's Association's Dementia and Brain Aging in Low- and Middle-Income Countries Conference, Nairobi, Kenya; the Alzheimer's Association international conference satellite symposium in Mexico City; and the ReD-Lat-Mexico Conference. N.U.O., in the past 36 months, reports receiving payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from the International Parkinson and Movement Disorders Society; support for attending the International Parkinson and Movement Disorders Society and the Global Parkinson's Genetics Program (GP2); and serving on the International Parkinson and Movement Disorders Society International Executive Committee and Africa Section Executive Committee and steering committee of GP2. S.M.P. reports receiving support from the Alzheimer's Association to attend the 2022 Alzheimer's Association's Dementia and Brain Aging in Low- and Middle-Income Countries Conference, Nairobi; and serving as executive member of Royal College of Psychiatrists Volunteering and International Psychiatry Special Interest Group (unpaid, conference organizer). R.R., in the past 36 months, reports receiving support from the Alzheimer's Association to attend meetings and/or travel and serving as the Alzheimer's Association San Diego/Imperial Chapter Board Chair (Unpaid). S.S., in the past 36 months, reports receiving consultation fees from Biogen and Eisai. P.H.S.G.H., in the past 36 months, reports receiving consultation fees from Transition-Bio; airfare to attend the 2022 Alzheimer's Association's Dementia and Brain Aging in Low- and Middle-Income Countries Conference, Nairobi; and serving on the Council of Governors, Cambridge University Hospitals. C.K.S., in the past 36 months, reports receiving support from the Alzheimer's Association to attend the meeting presented in this paper; serving as advisory council for ISTAART (unpaid) and having a leadership or fiduciary role in the Brazilian Society of Geriatrics and Gerontology (unpaid). P.T., in the past 36 months, reports receiving support for attending the 2022 Alzheimer's Association's Dementia and Brain Aging in Low- and Middle-Income Countries Conference, Nairobi. C.T.U.M., in the past 36 months, reports receiving consulting fees from the Brain and Mind Institute, Aga Khan University, Kenya; receiving a fellowship from the Alzheimer's Association and FINGERS Brain Health Institute to cover travel and accommodation to the 2022 Alzheimer's Association International Conference and the Dementia and Brain Aging in Low- and Middle-Income Countries Conference; and serving as (unpaid) committee member—NIH-sponsored National Academies of Science project to determine research priorities for Alzheimer's disease and related dementias, co-lead, global CEOi/Davos Alzheimer's Collaborative Workgroup on Implementation

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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